Table 1 Change in symptoms while taking azithromycin prophylaxis

	Mean	SD	SE	p value
Sputum volume	1.6	0.8	0.14	<0.001
Sputum colour	2.1	0.7	0.13	<0.001
Sputum consistency	2.5	0.6	0.11	0.006
Cough	2.4	0.7	0.12	0.001
Fatigue	2.1	1.0	0.18	0.001
Exercise tolerance	3.8	0.9	0.16	0.002
Wheeze	2.6	0.8	0.14	0.011
Breathlessness	2.3	0.7	0.13	0.002

Symptoms scored on a 5-point scale: 1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms.

S aureus (n = 1), *S pneumoniae* (n = 1). not done (n = 10). In three patients who had cultured *P aeruginosa* before starting azithromycin prophylaxis the organism was not recultured at follow up.

In the 33 patients completing at least 4 months treatment there was a statistically significant reduction in infective exacerbations requiring oral antibiotics from a mean of 0.71 per month to 0.13 per month ($p<0.001$). There was also a reduction in the requirement for intravenous antibiotics from a mean of 0.08 courses per month to 0.003 courses per month ($p<0.001$). Subgroup analysis of patients with *P aeruginosa* isolated before starting azithromycin prophylaxis showed no difference compared with all patients included ($p = 0.22$). Twenty five patients had lung function tests before and after at least 4 months of treatment (range 4–20 months). There was an improvement in all lung function parameters but the improvement in carbon monoxide transfer factor (TLCO) was the only one to reach statistical signficance ($p = 0.01$).

Symptom data were collected from 32 patients and scored on a 5-point scale (table 1). Statistical analysis using a non-parametric Wilcoxon test showed that there was a significant improvement in all symptoms.

The mechanism by which azithromycin reduces the number of infective exacerbations and chronic symptoms is unknown, but it is likely to be multifactorial. It may be due to downregulation of the host immune response by azithromycin, so decreasing host mediated tissue damage as postulated in the vicious circle hypothesis. It might also benefit patients by reducing bacterial load and therefore the stimulation for neutrophilic inflammation, or by influencing the pathogenic mechanisms of bacteria. Macrolide antibiotics have also been shown to reduce mucus secretion.[1 5]

Currie *et al* compared high dosage amoxicillin with placebo over an 8 month period and found a greater reduction in the volume of purulent sputum between exacerbations in the amoxicillin group (to 20% of pretreatment volume) than in the placebo group, but did not demonstrate any reduction in infective exacerbations.[6] The superior findings of our study suggest that the anti-inflammatory effects of azithromycin were important in achieving the results obtained. This study was performed with patients who were sufficiently unwell to preclude consideration of a placebo group. The patients therefore acted as their own controls. The results are sufficiently impressive to encourage the design of a randomised study, either enrolling less sick patients and having a placebo comparator or using a comparator antibiotic without immunomodulating properties.

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Early life antibiotics and asthma

Cullinan *et al*[1] present interesting data on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by prescriptions issued for respiratory illnesses, and the authors conclude that reverse causation was the likely explanation for this association.

The inappropriate use of antibiotics for respiratory symptoms caused by unrecognised asthma is the main potential confounding factor in observational studies attempting to demonstrate a causal link between antibiotic receipt and atopic illnesses. It is certainly plausible that GPs may prescribe antibiotics in children with symptoms such as cough and wheeze in early life. Suggestions of a casual link are strengthened by demonstration of an association when antibiotics were used for symptoms not associated with asthma. The earlier study by Farooqui and Hopkins[2] did, indeed, observe an association with non-respiratory use of antibiotics and asthma; in the study by Cullinan *et al* the association between non-respiratory indicated antibiotics and atopic asthma narrowly failed to reach statistical significance. The authors acknowledge that the study was only powered to show a doubling of the odds ratio for the association between early life antibiotic use and asthma, so an association remains possible in this cohort.

The most important limitation of the study, however, is the timing of the observed early life events in relation to secular changes in asthma prevalence and antibiotic prescribing, and hence the applicability of the results to modern day settings. This study observed events occurring 30 or more years ago in the parents of the Ashford birth cohort. As is well described, the prevalence of asthma has increased greatly over the last 30 years.[3] There may also have been significant increases in antibiotic prescribing over this time. The subjects in this study received an average of 3.1 and a median of 3 antibiotic prescriptions over 5 years, while we found in a recent case-control study[4] of 37 children with atopy and wheezing and 37 without either that the average and median number of antibiotic courses received during the first 5 years of life was 9.9 and 7 for wheezers and 6.3 and 5 for non-wheezers. There is also evidence of earlier prescribing of antibiotics in recent times; in our study group 89% of wheezers and 68% of non-wheezers received one or more courses of antibiotics in the first year, while in the Ashford study only 396 prescriptions were issued to 746 subjects in the first year, so a maximum of 53% children received any antibiotics.

It seems likely from the data presented that antibiotic exposure did not play a major causal role in promoting the asthma phenotype 30 years ago when both the prevalence of asthma and antibiotic prescribing to young children were significantly less than they are now, but the question of whether it may now be a significant and potentially modifiable factor remains unanswered.

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Recurrence of acute respiratory failure following use of waterproofing sprays

Between January and March 2003 six patients were admitted to hospital in the Lausanne area of Switzerland with acute respiratory failure following use of a waterproofing spray for clothes and leather. Within hours of exposure all patients developed a dry cough and rapidly progressive dyspnoea. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide

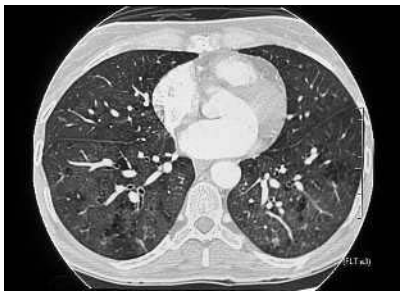

Figure 1 CT scan of thorax of a patient showing diffuse ground glass opacities.

transfer factor (TLCO). All patients had diffuse bilateral ground glass opacities on a high resolution CT scan, most often sparing the subpleural areas (fig 1). Every patient improved following treatment with oral prednisone (0.5–0.9 mg/kg) but residual dyspnoea and reduced TLCO (<80% of predicted value) could be seen for more than 2 weeks.

Acute respiratory failure was attributed to inhalation of the waterproofing spray in view of the sudden occurrence of symptoms following exposure, the diffuse ground glass opacities without other abnormalities on the CT scan, and the absence of any other detected cause. In particular, BAL fluid was sterile for bacteria, mycobacteria, viruses and fungi. Serological tests for chlamydia and mycoplasma were performed on two patients and were negative. A nasal swab for influenza was performed on one patient and was negative.

We were, however, surprised that the patients used three different spray brands. Waterproofing sprays contain three types of components—a propellant gas (propane butane), a waterproofing agent (fluorocarbon resin), and a solvent. It appeared that the manufacturer of the fluorinated resin changed during the summer of 2002 (the same for the three brands) and that the isopropanol solvent had to be replaced with a heptane solvent. Consumers started complaining of respiratory symptoms in October 2002 and the first severe case requiring admission was reported in January 2003. The three products were withdrawn from the market at the beginning of March. During this 6 month period 153 cases of respiratory symptoms related to waterproofing sprays were reported to the Swiss Toxicological Information Centre, whereas less than 10 cases per year had been reported in the previous 7 years.

The same fluorinated resin was also distributed in Germany, the Netherlands, and the UK. In Germany the waterproofing sprays were withdrawn before they reached the consumers. During the same period five patients were admitted to hospital in the Netherlands with the same complaints.[1] These sprays were also withdrawn from the Dutch market. Surprisingly, no case has yet been recorded in the UK.

However, only sprays for public use were withdrawn, not the industrial liquids. In Switzerland two additional patients developed a chemical pneumonitis with similar symptoms and diffuse bilateral ground glass opacities after using industrial waterproofing liquid with a nebuliser. Workers in the above mentioned countries should therefore be warned not to use the liquid form with nebulisers.

In the past, several outbreaks of acute respiratory symptoms have been recorded in different countries including 550 in Oregon in 1992,[2 3] in Pennsylvania and Virginia in 1993,[4] in Quebec in 1993,[5] and in Japan between 1992 and 1993.[6] Most of these epidemics followed a modification of the composition of the spray. One untreated patient developed a pulmonary fibrosis during a German outbreak in the 1980s[7] and one death was reported in Japan in the 1990s.[8]

Following these outbreaks, various suggestions were proposed to explain these intoxications.[9] In our opinion, the most likely explanation for the present outbreak is that the heptane solvent, which is more volatile than the previous one (isopropanol), allows the mist containing the new fluorinated resin to spread further in the tracheobronchial tree and to reach the alveoli where it might produce reactive metabolites inducing an alveolitis. However, the exact chemical reaction remains unknown. Because of the potentially lethal aspect of these intoxications and the possibility of new outbreaks, we consider that more research is needed on the effect of mist particle size and large analytical epidemiological studies are required to investigate this phenomenon further.

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Effect of PM_{10} on *H influenzae* and *S pneumoniae*

That air pollution, and specifically particles, are harmful to health is well accepted,[1] causing direct effects such as lung inflammation resulting in exacerbations of lung and cardiac conditions[2 3] and being associated with admissions for pneumonia. In the 1960s Lawther *et al* showed that ambient particles stimulated the growth of *Haemophilus influenzae* in vitro,[4] suggesting a direct effect of particles on bacteria themselves. However, it is not known whether this remains so for modern ambient particles where the sources are different.

To address this we have assessed the effect of PM_{10} (particles essentially less than 10 µm in diameter) on the respiratory pathogens commonly associated with acute exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia. The effect of dilutions of extracts of PM_{10} on the growth of *H influenzae* and *Streptococcus pneumoniae* grown in liquid broth and the effect of PM_{10} on microbial growth kinetics of *S pneumoniae* was assessed.

Fresh isolates of *H influenzae* and *S pneumoniae* obtained from clinical specimens and the control strains *H influenzae* NCTC 11931 and *S pneumoniae* ATCC 49619 were used. Particles were collected on a tapered element oscillating microbalance situated in central Birmingham, representative of an urban background site. To obtain a usable sample the surface of the filter was wetted and rinsed with two sequential aliquots of 0.5 ml saline using a Gilson pipette until visual inspection showed no more particles coming off the filter. The two aliquots were combined and sonicated for 2 minutes to disperse the particles and aggregates. This procedure usually gives a yield of 50–300 µg/ml particles (Donaldson, personal communication). It is not known for certain how these concentrations relate to likely concentrations in the epithelial lining fluid, but this approach has been used in previous in vitro studies of inflammatory responses which have shown pro-inflammatory effects.

In the first experiment a 1:20 dilution of PM_{10} was made by adding 0.5 ml to 9.5 ml Iso sensitest broth (ISTA; Oxoid Ltd, Basingstoke, UK) supplemented with 5% horse blood and 20 µg/ml NAD. The same volume of normal saline was added to controls. Test and control bottles were inoculated with 0.5 ml of organism suspension at a density of 0.5 Mcfarland. A viable count was performed hourly for 5 hours while incubating at 37℃ in 5% CO_2 using the Miles and Misra technique.[5] In the growth kinetic experiment equal volumes of PM_{10} solution and ISTA broth (supplemented with 5% lysed horse blood and 20 µg/ml NAD) were added to the first column of a sterile microtitre tray. Serial broth dilutions to a final dilution of 1:64 were performed. Control wells contained only broth and wells for sterility checks contained PM_{10} alone, broth alone and inoculum alone. Organism suspension, 50 µl *S pneumoniae* ATCC 49619, was added into each test and control column of the wells and incubated at 37℃ in 5% CO_2 for 5 hours. The Miles and Misra technique[5] was used to estimate the viable count of organism in each well and the differences in log cfu/ml between test and control were plotted against serial dilutions of PM_{10}. This test was repeated five times using the same strain to check for reproducibility.